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ORIGINAL ARTICLE

Longterm outcome of photodynamic therapy compared with biliary stenting alone in patients with advanced hilar cholangiocarcinoma

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Abstract

Objectives: This study aimed to determine longterm outcomes and factors associated with increased survival after photodynamic therapy (PDT) compared with endoscopic biliary drainage alone in patients presenting with advanced hilar cholangiocarcinoma (CC).

Methods: A retrospective analysis of the institutional database identifying all patients who presented with a diagnosis of hilar CC between December 1999 and January 2011 was conducted.

Results: Of the 232 patients identified, 72 (31%) were treated with PDT (Group A) and 71 (31%) were treated with endoscopic biliary drainage alone (Group B). Median survival was 9.8 months [95% confidence interval (CI) 7.42–12.25] in Group A and 7.3 months (95% CI 4.79–9.88) in Group B ($P = 0.029$). On multivariate analysis, biliary drainage without PDT ($P = 0.025$) and higher T-stage ($P = 0.002$) were significant predictors of shorter survival in all patients. In a subgroup analysis of patients in the PDT group, lower pre-PDT bilirubin level ($P = 0.005$), multiple PDT treatments ($P = 0.044$) and shortened time to treatment after diagnosis ($P = 0.013$) were significant predictors of improved survival. Median metal stent patency was longer in Group A than in Group B (215 days vs. 181 days; $P = 0.018$).

Conclusions: Photodynamic therapy with stenting resulted in longer survival than stenting alone. Early PDT after diagnosis and multiple PDT treatments were shown to have survival benefits. Metal stent patency was longer in patients receiving PDT. Higher T-stage appears to be a predictor of early mortality in advanced bile duct cancer treated with PDT.

Keywords

bile duct cancer, palliative endoscopic stenting, percutaneous transhepatic cholangioscopy, outcome, survival

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Introduction

Hilar cholangiocarcinoma (CC) is an uncommon neoplasm arising from the biliary confluence or the right or left hepatic ducts. The location of CC at the upper hepatoduodenal ligament, its extension into the liver and its proximity to major vascular structures render it difficult to evaluate before surgery and at laparotomy.[1]

Longterm control of biliary carcinomas can only be obtained by potentially curative surgery (i.e. the removal of all apparent tumours). However, because characteristic early symptoms are lacking, the disease is often at an advanced stage when a definitive diagnosis is established.[2] As a result, a large proportion of patients are beyond the scope of curative treatment on diagnosis and can be given only palliative management. In unresectable CC, usually the only therapeutic strategy is improvement of cholestasis by endoscopic or percutaneous drainage or a biliary bypass.[3,4] Although metal stent insertion improves occlusion rates and reduces the number of therapeutic interventions, it does not improve median survival time.[5] Attempts to affect tumour growth have been made with radiotherapy or chemotherapy. However, these therapies have not been demonstrated to prolong survival significantly.[6,7]

A treatment modality for local ablation of the primary tumour might improve the outcomes of curative as well as palliative therapies. Recently, there have been several promising reports of the outcomes of photodynamic therapy (PDT) as an advanced palliative strategy for CC, which have noted significant improvements in quality of life and survival after PDT and stenting.[8–10] However, the longterm outcome of PDT has not been determined. The aim of this study was to examine the longterm outcome and factors associated with increased survival after PDT compared with those after endoscopic biliary drainage alone in advanced hilar CC.

Materials and methods

Patients

A total of 232 patients with hilar CC treated between December 1999 and January 2011 were evaluated. Of these, 89 patients were excluded for reasons of surgery ($n = 38$), palliative chemotherapy or radiotherapy ($n = 30$), a Karnofsky performance status[11] of <60 ($n = 5$), percutaneous biliary drainage only ($n = 11$), loss from follow-up ($n = 4$), and sudden death during diagnostic workup ($n = 1$). Thus, data for 143 patients were available for further analysis. Of these patients, 72 (31%) were treated with PDT in addition to biliary stenting without chemoradiation (Group A) and 71 (31%) were treated with endoscopic stenting only (Group B) (Fig. 1). Patients were allocated to one of these treatment strategies based on their requirements after they had been informed of the efficacy, side-effects and cost of PDT. Clinical, laboratory, radiological, endoscopic and histopathological data were collected prospectively and analysed retrospectively. All patients included in this study were believed to be unresectable by accepted criteria.[12,13] The local institutional review board approved this retrospective study.

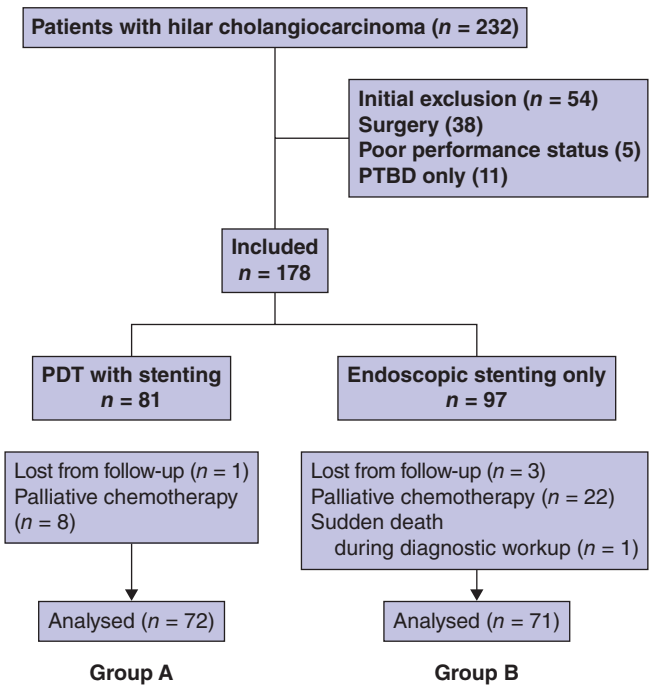

Figure 1 Flow chart showing participants included in and excluded from the current study. PTBD, percutaneous transhepatic biliary drainage; PDT, photodynamic therapy

Patients with unresectable hilar CC were offered PDT as a palliative modality if they consented to PDT with percutaneous transhepatic cholangioscopy (PTCS) or endoscopic retrograde cholangiopancreatography (ERCP). Based on the Bismuth–Corlette classification system,[14] patients were eligible if they demonstrated type IV lesions or advanced type III lesions containing T3 tumours. Patients with other type II or III tumours in whom surgery was contraindicated because of metastases, age >80 years or the presence of other comorbid conditions were also eligible. All patients were required to show a Karnofsky status of >60. All tumours were staged using the American Joint Committee on Cancer staging criteria (7th edition) for perihilar bile duct cancer.[15] All patients underwent a standard pretreatment evaluation that included thin-section, contrast-enhanced, multiphase spiral computed tomography (CT) and/or magnetic resonance imaging (MRI) of the abdomen. Resectability was defined according to the criteria of Vauthey and Blumgart.[16]

Photodynamic therapy

Photodynamic therapy was administered using previously described methods.[17,18] Briefly, patients received porfimer sodium (Photofrin II®; Axcan Pharma, Inc., Mont-Saint-Hilaire, QC, Canada) i.v. at a dose of 2 mg/kg at 48 h before endoscopic (ERCP) or percutaneous (PTCS) photoradiation. For light distribution, flexible cylindrical diffuser probes (BioLitec Pharma Ltd, Stirling, UK) mounted on 400-μm quartz fibres with an active distal tip length of 2 cm were used. The light source was a diode laser system (Ceralas PDT 633; CeramOptec GmbH, Bonn, Germany) with a maximum power output of 2 W and a wavelength of 633 ± 3 nm. The power emitted by the diffuser tip was calibrated to 400 mW/cm before PDT was administered using an integrating sphere power meter. The mean irradiation time was 452 s (range: 400–600 s), using a power density of 300–400 mW/cm and an energy dose of 180–200 J/cm (of diffuser length). To perform the percutaneous PDT procedure, a guidewire was first inserted through the stricture into the common bile duct. A 6-Fr guiding catheter was then inserted along the guidewire, permitting the guidewire to be removed. A diffuser fibre was then inserted into the guiding catheter and the stricture site was irradiated from the distal to the proximal region under cholangioscopy and fluoroscopy. Photodynamic therapy with PTCS was usually administered in more advanced Bismuth type III lesions. To perform PDT with ERCP, the preloaded catheter (catheter and PDT fibre) was advanced across the bile duct tumour using a 0.035-inch guidewire. The tip of the catheter contained a metal marker and was cut just below this marker to allow the fibre to pass. Tumour segments were treated sequentially in a proximal-to-distal fashion. After PDT was performed, 10-Fr plastic biliary stents were inserted to ensure

adequate decompression and bile drainage. Photodynamic therapy with ERCP was usually performed in cases of Bismuth type II, III or IV lesions and in patients aged >80 years.

Follow-up

Patients were followed up at 3-month intervals and were offered additional treatment with PDT, provided they were able to tolerate it and were willing to continue further treatment. Tumour response was assessed every 3 months with tumour markers [carbohydrate antigen 19-9 (CA19-9)] and imaging studies (ERCP, PTCS, MRI, chest radiography). Photodynamic therapy was repeated whenever follow-up biopsies were tumour-positive or when tumour progression was evident, based on ERCP, PTCS or MRI. As a practical rule, 10-Fr plastic endoprostheses were exchanged every 3–4 months to avoid occlusion and bacterial cholangitis. Enrolled patients were followed until death. The indications for metal stents were: age >80 years; refusal of additional PDT because of its high cost; referral from a distant location, and change to poor performance status during follow-up. Metal stent patency represented the time interval between stent insertion and replacement. If the patient died with a patent stent, the time interval was recorded as censored data. Successful drainage after technically successful stenting was defined as a >50% decrease in bilirubin level within 7 days of stenting.[19]

Statistical analysis

Statistical analyses were performed using SPSS Version 13.0 (SPSS, Inc., Chicago, IL, USA). Numerical data were presented as medians with ranges. Intergroup comparisons were performed using the Mann–Whitney *U*-test. Estimates of probabilities of survival for the follow-up study and cumulative stent patency were calculated using the Kaplan–Meier method with the log-rank test. Data were summarized as medians with 95% confidence intervals (CIs). For survival rates, all deaths related to CC and procedures were included, but deaths unrelated to CC were treated as censored. All data were analysed using an intention-to-treat analysis. Intention-to-treat survival was calculated from the day of treatment until death or the date of the last follow-up visit.

Cox regression was used to determine independent predictors of outcome, using survival as the dependent variable and significant factors ($P < 0.15$) determined by univariate analysis. *P*-values of ≤ 0.05 were deemed to indicate statistical significance.

Results

Baseline clinical and demographic profiles in the two treatment groups were similar, except in patients with Bismuth type IV lesions (Table 1). Group A included more patients with Bismuth type IV lesions than Group B (39/72 vs. 26/71; $P = 0.036$). There was no significant difference in age, gender, pre-procedure bilirubin level, CA19-9 level or tumour stage between the groups. Of the 72 patients in Group A, the PDT fibre was placed after the bile duct was accessed via PTCS in 59 (82%) patients and endoscopically (via ERCP) in 13 (18%) patients. The diagnosis was confirmed by histological analyses in 57 (79%) patients in Group A and 38 (54%) in Group B. Histological confirmation of malignancy in Group A was obtained by brush cytology in six ERCP patients and by intraductal biopsy examination in 51 PTCS patients. In Group B, histological confirmation was obtained by brush cytology in 25 ERCP patients, by intraductal biopsy in six direct cholangioscopy (mother–babyscope technique) patients, and by percutaneous ultrasonography-guided biopsy in seven patients. Patients received a total of 99 PDT treatments (median = 1; range: 1–4). Overall, 51 (71%), 16 (22%), four (6%) and one (1%) patient received one, two, three or four PDT treatments, respectively.

Successful drainage was achieved in 92% and 83% of patients in Groups A and B, respectively. Median bilirubin levels before the start of therapy in Groups A and B were 11.3 mg/dl (range: 0.9–27.6 mg/dl) and 10.5 mg/dl (range: 0.8–32.9 mg/dl), respectively. At 7 days, median bilirubin levels in Groups A and B had decreased to 2.8 mg/dl (range: 0.4–12.6 mg/dl) and 3.6 mg/dl (range: 0.3–11.4 mg/dl), respectively. No significant difference was observed in the degree of decrease in bilirubin level between the two groups ($P = 0.131$).

Eighteen patients in Group A (25%) and 15 patients in Group B (21%) underwent biliary drainage with plastic stent insertion followed by the placement of a self-expanding metal stent (Group A: plastic stent before metal stent, $n = 13$, percutaneous transhepatic biliary drainage before metal stent, $n = 5$; Group B: plastic stent before metal stent, $n = 15$). In a subgroup analysis of patients in whom a metal stent was inserted, duration of stent patency was longer in Group A than in Group B (Fig. 2). The median stent patency was 215 days (range: 72–570 days) in Group A and 181 days (range: 70–209 days) in Group B ($P = 0.018$).

Survival

The median follow-up periods from diagnosis to death in Groups A and B were 11.3 months (range: 2.4–44.3 months) and 9.1 months (range: 0.9–34.6 months), respectively ($P = 0.038$). Kaplan–Meier survival analysis showed a significantly longer survival time in Group A (PDT) compared with the endoprostheses group (Fig. 3). Median survival was 9.8 months (95% CI 7.42–12.25) in Group A and 7.3 months (95% CI 4.79–9.88) in Group B ($P = 0.029$). The 1-, 2- and 3-year survival rates were 39.4%, 13.9% and 4.1% in Group A and 26.6%, 9.4% and 0% in Group B, respectively.

Kaplan–Meier survival curves according to tumour stage are illustrated in Fig. 4. One-year survival was 75.0% in stage II, 36.3% in stage III (IIIa/IIIb) and 24.2% in stage IV (IVa/IVb) disease. Median survival was 14.5 months (95% CI 12.89–16.17) in stage II, 9.4 months (95% CI 7.40–11.34) in stage III and 7.6 months (95% CI 6.13–9.13) in stage IV disease.

At the end of the observation period, all patients in Group A had died and only one patient in Group B remained alive. Causes of death in Group A patients were tumour progression (61%,

Table 1 Characteristics of patients in Groups A (photodynamic therapy with stenting) and B (stenting only)

	Group A (*n* = 72)	Group B (*n* = 71)
Age, years, median (range)	62.5 (36–89)	67 (42–85)
Male sex, *n* (%)	46 (64)	49 (69)
AJCC stage[a], *n* (%)		
II	8 (11)	5 (7)
IIIa/IIIb	9 (13)/21 (29)	9 (13)/20 (28)
IVa/IVb	20 (28)/14 (19)	17 (24)/20 (28)
Bismuth type, *n* (%)		
II	6 (8)	16 (23)
IIIa/IIIb	9 (13)/18 (25)	20 (28)/9 (13)
IVa/IVb	25 (35)/14 (19)	6 (8)/20 (28)
Liver metastasis, *n* (%)	10 (14)	12 (17)
CA19-9, U/ml, median (range)	711.6 (0.9–4800)	925.5 (1.36–4800)
Bilirubin, mg/dl, median (range)		
Pretreatment	9.9 (0.6–34.8)	11.6 (0.5–32.9)
Post-treatment	1.8 (0.3–14.3)	3.1 (0.3–29.8)
Pre-PDT albumin, g/dl, median (range)	3.5 (2.0–4.5)	3.4 (2.0–4.6)
PDT method, *n* (%)		
PTCS	59 (82)	
ERCP	13 (18)	
Type of stent, *n* (%)		
Plastic	54 (75)	56 (79)
Metal	18 (25)	15 (21)

[a]American Joint Committee on Cancer, 7th edition.
CA19-9, carbohydrate antigen 19-9; PDT, photodynamic therapy; PTCS, percutaneous cholangioscopy; ERCP, endoscopic retrograde cholangiopancreatography.

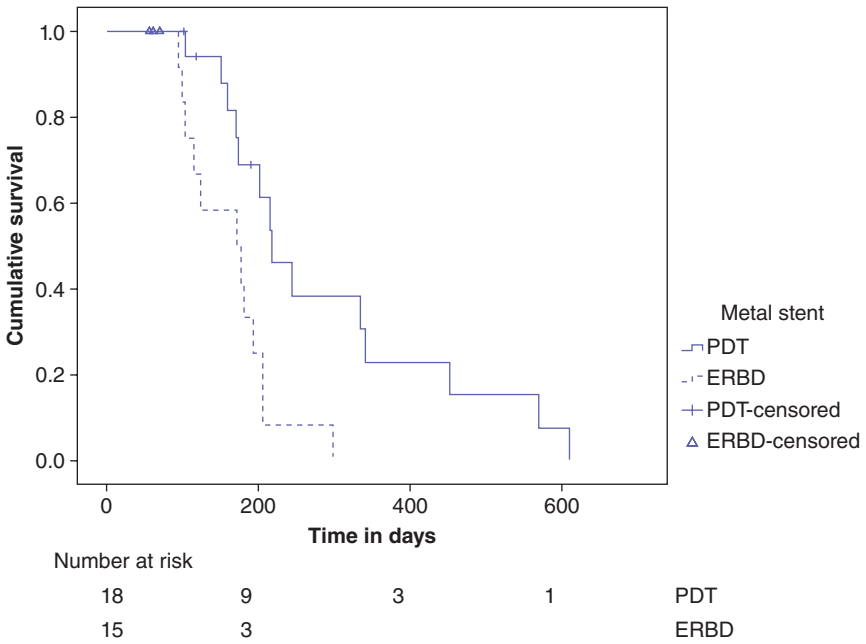

Figure 2 Kaplan–Meier estimation of metal stent patency rates in Groups A and B. Median stent patency was longer in Group A (215 days) than in Group B (181 days) ($P = 0.018$). PDT, photodynamic therapy; ERBD, endoscopic retrograde biliary drainage

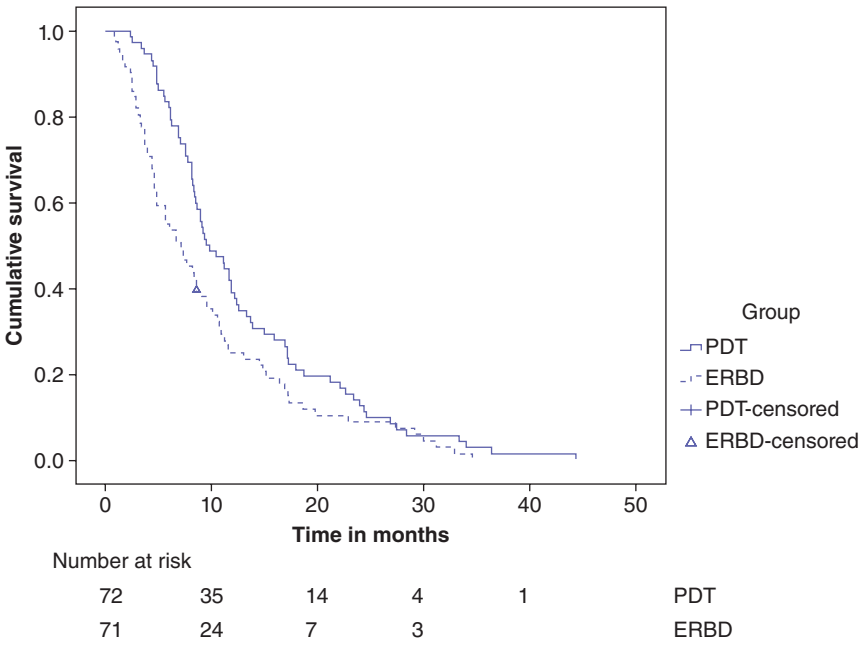

Figure 3 Kaplan–Meier curves showing overall survival in Group A [photodynamic therapy (PDT) with stenting] and Group B (stenting only). Median survival was 9.8 months [95% confidence interval (CI) 7.42–12.25] in Group A and 7.3 months (95% CI 4.79–9.88) in Group B (P = 0.030). ERBD, endoscopic retrograde biliary drainage

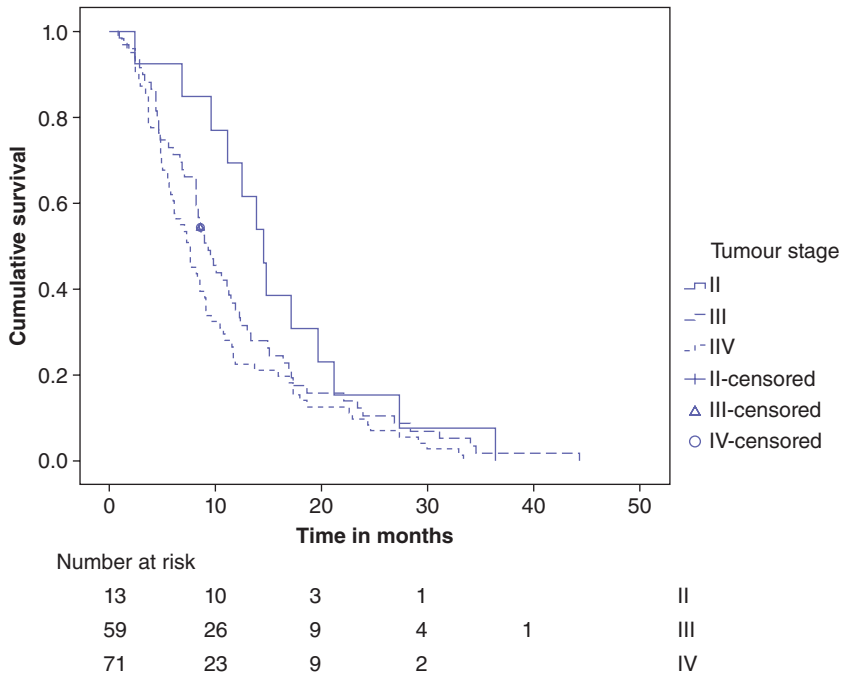

Figure 4 Kaplan–Meier curves showing survival according to tumour stage. Median survival after diagnosis was longer in patients with stage II disease (14.5 months) than patients with stage IV disease (7.6 months) (P = 0.036), but did not differ significantly between patients with stage II (14.5 months) and stage III (9.4 months) disease (P = 0.166)

Table 2 Results of univariate and multivariate analyses of all prognostic factors associated with survival in all patients

Variable	Univariate (Kaplan–Meier and log-rank test)			Multivariate (Cox proportional hazards model)[a]		
	Cases	Median survival, months	*P*-value	HR	95% CI	*P*-value
Age, years						
<65 vs. ≥65	68:75	9.2:8.5	0.331			
Gender						
Male vs. female	95:48	9.6:8.6	0.359			
CA19-9, U/ml						
<100 vs. ≥100	38:102	13.0:8.4	0.047	1.35	0.910–1.995	0.136
Serum albumin, g/dl						
<3.5 vs. ≥3.5	73:70	8.2:9.6	0.198			
Pre-PDT bilirubin, mg/dl						
<3.0 vs. ≥3.0	43:100	11.6:8.1	0.005	1.26	0.852–1.881	0.244
Tumour stage[b]						
T2 vs. T3, T4	37:106	11.6:8.2	0.004	1.93	1.261–2.937	0.002
Lymph node involvement						
Yes vs. No	95:48	9.5:8.6	0.943			
Bismuth type						
II, III vs. IV	78:65	9.1:8.6	0.649			
Treatment group						
PDT vs. ERBD	72:71	9.8:7.2	0.029	1.53	1.056–2.221	0.025

[a]Factors were included in multivariate analysis if $P < 0.05$ in univariate analysis.
[b]American Joint Committee on Cancer, 7th edition.
HR, hazard ratio; 95% CI, 95% confidence interval; CA19-9, carbohydrate antigen 19-9; PDT, photodynamic therapy; ERBD, endoscopic retrograde biliary drainage.

$n = 44$), acute liver failure (22%, $n = 16$), biliary sepsis (11%, $n = 8$), and non-CC-related causes (6%; variceal bleeding $n = 1$, lung cancer $n = 1$, heart disease $n = 2$). Causes of death in Group B were tumour progression (66%, $n = 46$), acute liver failure (11%, $n = 8$), biliary sepsis (20%, $n = 14$) and variceal bleeding (3%, $n = 2$). Chronic cholangitis led to secondary biliary cirrhosis and fatal complications, such as variceal bleeding, in three patients without tumour progression.

Prognostic factors analysis

Table 2 shows the results of univariate and multivariate analysis of all variables associated with survival in all patients. Levels of CA19-9 [hazard ratio (HR) = 1.47, 95% CI 1.003–2.613; $P = 0.047$] and bilirubin (HR = 1.65, 95% CI 1.139–2.401; $P = 0.005$) at diagnosis, T-stage (HR = 1.80, 95% CI 1.205–2.679; $P = 0.004$) and treatment group (HR = 1.46, 95% CI 1.037–2.046; $P = 0.029$) were statistically significant predictors of survival on univariate analysis. Findings regarding tumour stage showed that survival after diagnosis was longer in stage II patients than in stage IV patients (median survival: 14.5 months vs. 7.6 months; $P = 0.036$), but did not significantly differ between stage II and III patients (median survival: 14.5 months vs. 9.4 months, respectively; $P = 0.166$). Factors including lower serum albumin level before treatment, gender, Bismuth type, PDT method (PTCS vs. ERCP) and lymph node involvement did not significantly affect survival according to univariate analyses. Multivariate analysis using Cox regression in all patients showed that lack of biliary drainage and higher T-stage were significant predictors of shorter survival in advanced hilar CC. A subgroup analysis of Group A (PDT group) data (Table 3) showed that increased time to treatment after diagnosis (Fig. 5), a higher pretreatment bilirubin level and a single PDT treatment were statistically significant predictors of shorter survival after PDT.

Adverse events

It is not possible to differentiate clinically between cholangitis induced by tumour progression and that induced by the endoscopic procedure; thus the incidence of cholangitis was not compared between the two groups. In Group A, hyperpigmentation of the skin occurred in 10 patients (14%) and cutaneous complications, including erythema or facial oedema, were seen in one patient, but skin abnormalities improved with conservative treatment. Biliary leakage occurred in one of 99 PDT treatments. Sepsis occurred in one patient after the second PDT treatment. A liver abscess occurred in one patient after an initial PDT treatment with PTCS; further PDT was stopped and supportive care was given. With respect to complications related to the PTCS tube, tube breakage, bile leakage from the tube insertion site and premature exchange of the PTCS tube as a result of early tube occlusion occurred in one, two and three patients, respectively.

Table 3 Results of univariate and multivariate analyses of all prognostic factors associated with survival in patients receiving photodynamic therapy

Variable	Univariate (Kaplan–Meier and log-rank test)			Multivariate (Cox proportional hazards model)[a]		
	Cases	Median survival, months	*P*-value	HR	95% CI	*P*-value
Age, years						
<65 vs. ≥65	42:30	9.1:11.2	0.809			
Gender						
Male vs. female	46:26	11.7:9.1	0.621			
CA19-9, U/ml						
<100 vs. ≥100	22:49	12.2:9.1	0.760			
Serum albumin, g/dl						
<3.5 vs. ≥3.5	35:37	8.6:11.7	0.830			
Pre-PDT bilirubin, mg/dl						
<3.0 vs. ≥3.0	30:42	11.9:8.5	0.012	2.25	1.337–3.798	0.002
Tumour stage[b]						
T2 vs. T3, T4	18:54	11.2:9.4	0.244			
Lymph node involvement						
Yes vs. No	46:26	9.8:9.3	0.518			
Bismuth type						
II, III vs. IV	33:39	10.4:9.2	0.977			
PDT method						
PTCS vs. ERCP	59:13	9.8:9.3	0.719			
Time to PDT after diagnosis, months						
<3 vs. ≥3	54:18	11.9:9.1	0.034	2.11	1.173–3.795	0.013
Number of PDT treatments						
1 vs. ≥2	51:21	8.7:12.2	0.048	1.79	1.044–3.083	0.034

[a]Factors were included in multivariate analysis if $P < 0.05$ in univariate analysis.
[b]American Joint Committee on Cancer, 7th edition.
HR, hazard ratio; 95% CI, 95% confidence interval; CA19-9, carbohydrate antigen 19-9; PDT, photodynamic therapy; PTCS, percutaneous cholangioscopy; ERBD, endoscopic retrograde biliary drainage.

In Group B, stent migration subsequent to cholangitis occurred in 11 patients (16%; one metal stent and 10 plastic stents). Two patients developed an infected biloma with prolonged cholangitis after endoprostheses and were managed with antibiotic treatment.

Discussion

Complete surgical resection remains the foundation of therapy with curative intent in patients with extrahepatic CC, but because of its anatomic location and natural history, the disease is locally advanced in most patients at the time of diagnosis. Patients with unresectable CC have few therapeutic options other than palliative biliary stenting. Although metal stent insertion improves occlusion rates and reduces the number of therapeutic interventions, it does not extend median survival.[5] Chemotherapy is widely regarded as ineffective for biliary tract cancer. A meta-analysis of 2810 patients in 104 mostly small, non-randomized studies reported a median response rate of 23% and a small survival advantage (1 month) in those undergoing chemotherapy, particularly using gemcitabine and platinum-based regimens.[20] A treatment modality for local ablation of the primary tumour might improve the outcomes of curative and palliative therapies. Palliative brachytherapy with 192-iridium alone (35 Gy at a 1-cm distance) did not prolong median survival time (4.3–5.0 months),[21] but, when combined with external beam radiotherapy (30 Gy), this treatment did result in median survival times of 10.0–10.5 months.[22] Another modality for local tumour ablation of CC is PDT. Even in patients with advanced disease, PDT has been shown to improve survival, quality of life and performance status, compared with biliary stenting, in uncontrolled[8,23] and randomized controlled trials.[10,24] The overall median survival after PDT in the current study was 9.8 months, which is similar to rates in previous reports.[8,25]

A subgroup analysis in the PDT group showed a high pretreatment bilirubin level to be strongly related to poor survival. Effective palliation is essential because biliary drainage and prevention of cholestasis are crucial to prevent pruritus, cholangitis and death. The approach to palliative decompression has evolved from surgery and percutaneous to endoscopic management with the aim of preventing cholestasis and improving mortality rates.

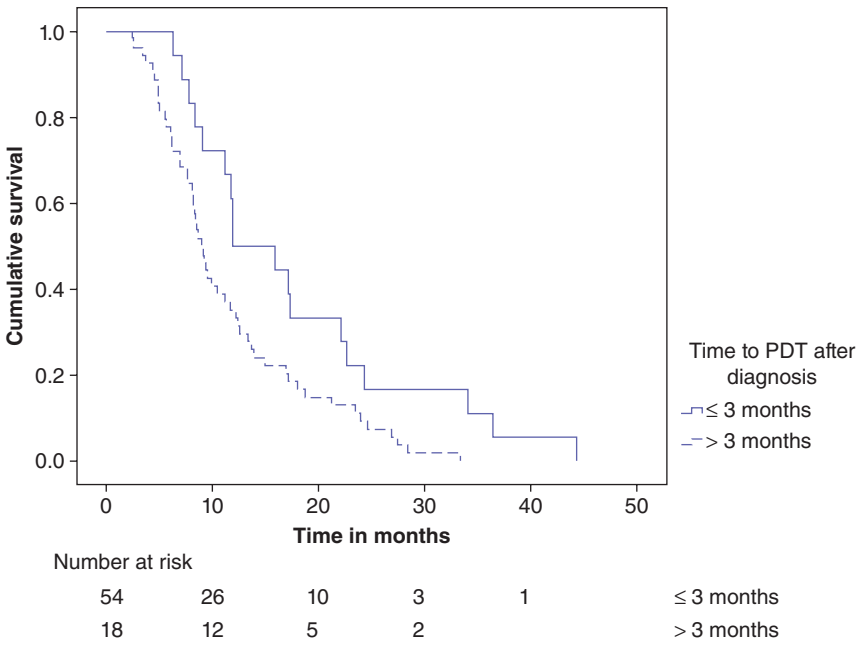

Figure 5 Kaplan–Meier curves showing overall survival [from date of photodynamic therapy (PDT) to death or last follow-up evaluation]. Median survival was 11.9 months [95% confidence interval (CI) 6.09–17.64] in patients in whom the time from diagnosis to PDT was ≤3 months and 9.1 months (95% CI 7.88–10.32) in patients in whom the time from diagnosis to PDT was >3 months ($P = 0.022$)

Unfortunately, the benefit of ERCP with stent placement is often obviated by proximal tumour obstruction.[26,27] To address this issue, multiple studies have investigated the effects of combining bile duct stent insertion with PDT.[8,10,23] Photodynamic therapy offers the possibility of 'remodelling' the tumoral mass,[28] which may enhance or prolong the decompressive effect.

T-stage was an independent predictor of survival on multivariate analysis in all patients with hilar CC, although it was not significant in subgroup analysis of the PDT group. Another study demonstrated efficient selective tumour destruction of CC within a superficial 4-mm layer.[28] Therefore, PDT with haematoporphyrin derivatives [porfimer sodium (Photofrin II®; Axcan Pharma, Inc.)] in localized hilar CC will not be potentially curative until the procedure can be improved to exert selective tumour destruction for a wall thickness of 8–10 mm.

In a subgroup analysis of patients in whom metal stents were inserted, the duration of stent patency was longer in Group A than in Group B. Median stent patency was 215 days in Group A and 181 days in Group B ($P = 0.018$). One of the main causes of the obstruction of metal stents in bile duct cancer is tumour ingrowth or overgrowth.[29] In particular, the duration of metal stent patency in hilar CC is shorter than in distal bile duct cancer.[19,26] Thus, the effect of PDT in destroying cancer and neovascular cells induced the prolongation of stent patency. However, further randomized studies are needed to confirm this.

Survival in patients who received multiple PDT treatments was significantly longer than that in patients who underwent a single PDT treatment in univariate analysis. The authors have previously examined the potential value of monthly follow-up evaluations using intraductal ultrasonography (IDUS) to assess response to PDT in hilar CC.[17] Three months after PDT, the mean thickness of the tumour mass had significantly decreased, and the mean thickness of the tumour had increased at 4 months after PDT.[17] Based on these findings, it was recommended that PDT in advanced hilar CC be repeated every 3 months.[17] However, many of the patients in this study were referred from distant places and were of poor economic status, which made it difficult for them to return for subsequent treatments. A major obstruction to repeated treatment was the high cost of PDT. Thus, if the cost of PDT could be lowered, multiple sessions of PDT would become possible and a subsequent improvement in survival rates might be expected.

Extrabiliary spread, such that involving lymph nodes, vascular invasion or encasement, and distant metastases, was not shown to be a significant predictor of survival in this study. More than 50% of the patients in this study demonstrated extrabiliary spread.

Time from diagnosis to treatment with PDT was a significant factor not only in univariate analysis, but also in multivariate analysis. Similar findings were reported in another study.[30] The negative effect of a prolonged time interval from diagnosis to treatment on survival reflects a progressively increasing tumour burden. This study indicated that for maximal survival benefit with PDT, patients should be treated as soon as possible after a diagnosis of unresectable CC is confirmed. Earlier treatment may prevent a subsequent delay caused by biliary obstruction, as well as loss of hepatic function.

This study was limited by the retrospective nature of its design. However, the study population was derived from a larger cohort of

patients with CC and patients were followed until death. Median survival in this cohort was comparable with that in other cohorts reported in the literature. Additional PDT (i.e. local ablative therapy) and systemic chemotherapy may create a synergistic effect that improves survival and quality of life in advanced bile duct cancer. Thus, further prospective randomized controlled studies comparing outcomes of chemotherapy with PDT and chemotherapy alone are required to confirm the role of PDT in advanced bile duct cancer.

In summary, PDT with stenting resulted in longer survival than stenting alone. Survival was also improved by the provision of early PDT after diagnosis and multiple PDT treatments. Metal stent patency was longer in patients receiving PDT. A higher T-stage appears to be a predictor of early mortality in advanced bile duct cancer treated with PDT.

Conflicts of interest

None declared.

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